



Year: 1998

Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996

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Abstract: OBJECTIVES: Published reports were reviewed to evaluate the characteristics of peripartal management and the late pregnancy outcome in women with pulmonary vascular disease (PVD). **BACKGROUND:** Pulmonary hypertension poses one of the highest risks for maternal mortality, but actual data on the maternal and neonatal prognosis in this group are lacking. **METHODS:** Reports published from 1978 through 1996 of Eisenmenger's syndrome (n = 73), primary pulmonary hypertension (PPH) (n = 27) and secondary vascular pulmonary hypertension (SVPH) (n = 25) complicating late pregnancy were included and analyzed using logistic regression analysis. **RESULTS:** Maternal mortality was 36% in Eisenmenger's syndrome, 30% in PPH and 56% (p < 0.08 vs. other two groups) in SVPH. Except for three prepartal deaths due to Eisenmenger's syndrome, all fatalities occurred within 35 days after delivery. Neonatal survival ranging from 87% to 89% was similar in the three groups. Previous pregnancies, timing of the diagnosis and hospital admission, operative delivery and diastolic pulmonary artery pressure were significant univariate (p < 0.05) maternal risk factors. Late diagnosis (p = 0.002, odds ratio 5.4) and late hospital admission (p = 0.01, odds ratio 1.1 per week of pregnancy) were independent predictive risk factors of maternal mortality. **CONCLUSIONS:** In the last two decades maternal mortality was comparable in patients with Eisenmenger's syndrome and PPH; however, it was relevantly higher in SVPH. Maternal prognosis depends on the early diagnosis of PVD, early hospital admission, individually tailored treatment during pregnancy and medical therapy and care focused on the postpartal period.

DOI: [https://doi.org/10.1016/S0735-1097\(98\)00162-4](https://doi.org/10.1016/S0735-1097(98)00162-4)

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-113321>

Journal Article

Published Version



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Originally published at:

Weiss, B M; Zemp, L; Seifert, Burkhardt; Hess, O M (1998). Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *Journal of the American College of Cardiology*, 31(7):1650-1657.

DOI: [https://doi.org/10.1016/S0735-1097\(98\)00162-4](https://doi.org/10.1016/S0735-1097(98)00162-4)

Outcome of Pulmonary Vascular Disease in Pregnancy: A Systematic Overview From 1978 Through 1996

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Objectives. Published reports were reviewed to evaluate the characteristics of periparturient management and the late pregnancy outcome in women with pulmonary vascular disease (PVD).

Background. Pulmonary hypertension poses one of the highest risks for maternal mortality, but actual data on the maternal and neonatal prognosis in this group are lacking.

Methods. Reports published from 1978 through 1996 of Eisenmenger's syndrome (n = 73), primary pulmonary hypertension (PPH) (n = 27) and secondary vascular pulmonary hypertension (SVPH) (n = 25) complicating late pregnancy were included and analyzed using logistic regression analysis.

Results. Maternal mortality was 36% in Eisenmenger's syndrome, 30% in PPH and 56% (p < 0.08 vs. other two groups) in SVPH. Except for three preparturient deaths due to Eisenmenger's syndrome, all fatalities occurred within 35 days after delivery. Neonatal survival ranging from 87% to 89% was similar in the

three groups. Previous pregnancies, timing of the diagnosis and hospital admission, operative delivery and diastolic pulmonary artery pressure were significant univariate (p < 0.05) maternal risk factors. Late diagnosis (p = 0.002, odds ratio 5.4) and late hospital admission (p = 0.01, odds ratio 1.1 per week of pregnancy) were independent predictive risk factors of maternal mortality.

Conclusions. In the last two decades maternal mortality was comparable in patients with Eisenmenger's syndrome and PPH; however, it was relevantly higher in SVPH. Maternal prognosis depends on the early diagnosis of PVD, early hospital admission, individually tailored treatment during pregnancy and medical therapy and care focused on the postparturient period.

(J Am Coll Cardiol 1998;31:1650-7)

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Preexistence or gestational occurrence of pulmonary vascular disease (PVD) is one of the rare conditions unequivocally considered to pose an extreme risk of maternal death. The poor tolerance during pregnancy seems to result from a low, pregnancy-independent exercise capacity superimposed on the gestational cardiovascular demands, insufficient adaptation of the right heart and poorly compliant pulmonary vasculature (1-5). Pregnancy prevention and early interruption became and still are the relevant measures for improving long-term survival in women of childbearing age with PVD (6). The last large-scale review of outcome in pregnant women with Eisenmenger's syndrome was published in 1979 (7); however, actual data on the outcome of late pregnancy in women with other types of PVD are lacking. Published reports from the two decades were reviewed to evaluate the influence of periparturient management and outcome of late pregnancy in women with PVD.

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Manuscript received September 17, 1997; revised manuscript received February 23, 1998, accepted March 4, 1998.

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Methods

Material selection. The data base of the National Library of Medicine (MEDLINE) was used to identify the cases, published in any language from January 1978 to December 1996, of PVD complicating late pregnancy. The key words *pregnancy*, *pulmonary hypertension*, *primary pulmonary hypertension* (PPH), *pulmonary vasculitis*, *pulmonary vascular disease*, *congenital heart disease*, *Eisenmenger's complex* and *Eisenmenger's syndrome* were used. The reference list of all journal articles and recent book chapters was reviewed. The cases of late pregnancy (beyond 22 weeks and described with the intention to continue the pregnancy) were separated from reports of spontaneous abortion or pregnancy interruption. Only the last reported pregnancy was included in the analysis. Other types of secondary PVD (e.g., acquired heart, chronic lung or chest wall diseases) were rejected on an a priori basis. Eisenmenger's syndrome was considered if congenital heart disease, a shunt at any level and pulmonary hypertension (irrespective of the numerical values) were present. From one monocentric study (8), only patients with an established diagnosis were included; other cases, reported years before the definitive diagnosis was made, were excluded (8). PPH was considered if none of the concomitant causes, diseases or assumed triggers of pulmonary hypertension (9) was mentioned. Secondary vascular pulmonary hypertension (SVPH) comprised a heterogeneous group of patients with the history

Abbreviations and Acronyms

CI	= confidence interval
OR	= odds ratio
PAP	= pulmonary artery pressure
PPH	= primary pulmonary hypertension
PVD	= pulmonary vascular disease
SaO ₂	= arterial oxygen saturation of hemoglobin
SVPH	= secondary vascular pulmonary hypertension

or presence of various concomitant diseases, assumed or recognized triggers and/or autopsy findings of PVD. In some, pulmonary hypertension was connected with the use of incriminated drugs, in others it was of congenital origin (peripheral pulmonary artery stenoses) or resulted from thromboembolism, hepatitis, systemic connective tissue or vascular inflammatory disease. These cases were grouped together independent of etiopathogenesis of PVD and labeled SVPH.

Data analysis. Patient characteristics were presented for each group, and the details of periparturient management were separated by maternal outcome. Data were presented as the number (%) per group, mean value \pm SD and range or, when appropriate, as median and range. Maternal and fetal/neonatal mortality or survival were presented as the number (%) of deaths and exact 95% confidence intervals (CI) for each PVD group. Logistic regression analysis (SPSS for Windows, Release 6.0.1., SPSS Inc.), with maternal outcome as the dependent variable, was used univariately for each group and for all cases. Independent covariates included age, gravida, para, timing of the diagnosis (before pregnancy vs. late diagnosis, if PVD was found during pregnancy or after delivery), week of pregnancy at hospital admission, pulmonary artery pressure (PAP), hemoglobin and arterial oxygen saturation of hemoglobin (SaO₂) values during pregnancy, timing of delivery, mode of delivery (vaginal vs. operative), type of monitoring (invasive vs.

noninvasive), type of anesthesia (general vs. regional) and use or nonuse of a pulmonary artery catheter, oxytocic drugs and antithrombotic drugs. When neonatal outcome was analyzed as the dependent variable, maternal outcome was included in the independent covariates. A p value <0.1 indicated a trend or potential risk factor. A p value <0.05 was considered statistically significant, and the odds ratio (OR) with 95% CI was calculated to express the predictive relative risk. For continuous and counting data, risk was expressed per unit of measurement. Multivariate (stepwise forward) logistic regression analysis was used to identify the independent risk factors of maternal mortality. The limit to enter an item into the multivariate analysis was p < 0.05 in the univariate analysis.

Results

Eisenmenger's syndrome. The patient characteristics (8,10-60) are summarized in Table 1, and the anatomic defects are presented in Table 2. Worsening of dyspnea and cyanosis and, occasionally, hemoptysis, cerebrovascular attack, syncope, chest pain, atrial fibrillation or premature uterine contractions were indications for hospital admission during pregnancy. Treatment consisted of bed rest and oxygen supplementation, digoxin (rarely), calcium antagonists and, to suppress premature uterine contractions or preeclampsia, magnesium. Three patients died during pregnancy (23,41). Of 70 remaining patients, 33 (47%) delivered at term (≥ 37 weeks), 23 (33%) delivered between weeks 32 and 36 and 14 (20%) delivered ≤ 31 weeks. Periparturient management is presented in Table 3. Hypoxemia, pulmonary hypertensive crisis and systemic hypotension (in two cases due to oxytocic drugs), bradycardia, pulmonary thromboembolism, cerebrovascular attack, convulsions, bleeding with or without anticoagulant therapy, peripheral vein thrombosis and concomitant periparturient cardiomyopathy influenced postparturient recovery. Vasoactive

Table 1. Characteristics of Parturients With Pulmonary Vascular Disease

	Eisenmenger's Syndrome (n = 73)	Primary Pulmonary Hypertension (n = 27)	Secondary Vascular Pulmonary Hypertension (n = 25)
Gravida*	1 (1-4)	2 (1-3)	2 (1-7)
Para ≥ 1 *	1 (1-3)	2 (1-3)	3 (1-5)
n (%)	17 (23%)	14 (52%)	13 (52%)
Diagnosis made†			
Before pregnancy	59 (81%)	7 (26%)	6 (24%)
During pregnancy	11 (15%)	14 (52%)	12 (48%)
Postpartum	3 (4%)	6 (22%)	7 (28%)
Hospital admission (weeks of pregnancy)‡	28.3 \pm 6.7 (10-40)	27.6 \pm 5.6 (15-36)	32.4 \pm 5.1 (21-39)
At term before delivery†	9 (13%)§	0	6 (24%)
SaO ₂ (%)‡	84.8 \pm 6.6 (67-98)	91.1 \pm 7.0 (70-98)	91.4 \pm 4.5 (82-96)
Hgb (g/dl)‡	15.7 \pm 2.5 (10.2-20.4)	Not reported	11.5 \pm 2.2 (8.9-15.9)
PAP, systolic (mm Hg)‡	108.0 \pm 25.5 (55-160)	85.3 \pm 20.4 (50-135)	82.9 \pm 27.9 (30-135)
PAP, diastolic (mm Hg)‡	55.2 \pm 19.7 (12-100)	44.4 \pm 13.2 (25-70)	37.4 \pm 17.9 (5-70)

Data presented are *median value (range); †number (%) of patients; or ‡mean value \pm SD (range). §n = 70. Hgb = hemoglobin concentration during pregnancy (n = 49); PAP = pulmonary artery pressure during pregnancy (systolic value, n = 81; diastolic value, n = 70); SaO₂ = arterial oxygen saturation of hemoglobin during pregnancy (n = 73).

Table 2. Anatomic Defects of Eisenmenger's Syndrome (n = 73)

Isolated ventricular septal defect*†	35 (48%)
Isolated atrial septal defect*	13 (18%)
Isolated patent ductus arteriosus	7 (9%)
Atrial and ventricular septal defect, atrioventricular canal*	5 (7%)
Truncus arteriosus, aortopulmonary window*	3 (4%)
Patent ductus arteriosus with atrial or ventricular septal defect	2 (3%)
Transposition of the great arteries with single ventricle or atrial and ventricular septal defect*	2 (3%)
Pulmonary atresia with ventricular septal defect and aortopulmonary collateral channels	2 (3%)
Tetralogy of Fallot, Pott's anastomosis*	1 (1%)
Not defined	3 (4%)

*In nine patients a cardiac surgical procedure was performed at various intervals before pregnancy. †In four patients an isolated ventricular septal defect was surgically closed in childhood. Data presented are number (%) of patients.

drugs, oxygen supplementation, blood transfusion, cessation or start of anticoagulant therapy, reoperation and hysterectomy or repair of an atrial septal defect were required postpartum. Of 26 fatalities (36%) (Fig. 1), 23 women died within 30 days after delivery (12,13,15,21,22,24,25,27,32-35,37-41,47,51,54). The cause of death was described as pulmonary hypertensive crisis with therapy-resistant heart failure (n = 13), unspecific "sudden" death (n = 7), autopsy-confirmed pulmonary throm-

Table 3. Management and Outcome of Pregnant Women With Eisenmenger's Syndrome (n = 73)

	Maternal Survival	Maternal Mortality
No. (%)	47 (64%)	26 (36%)
95% CI	52-75	25-48
Age (years)*	26.4 ± 4.8 (18-37)	24.9 ± 4.5 (18-33)
Hospital admission (weeks of pregnancy)*	26.7 ± 6.5 (10-39)	31.4 ± 5.9 (21-40)
Toxemia of pregnancy†	2 (4%)	3 (12%)
Delivery (weeks of pregnancy)*	35.1 ± 3.5 (26-40)	34.4 ± 4.4 (26-40)
Vaginal delivery†	27 (57%)	11 (48%)
Operative delivery†	20 (43%)	12 (52%)
Monitoring		
Noninvasive, not reported†	24 (51%)	15 (63%)
Invasive SAP and/or CVP†	23 (49%)	9 (37%)
Invasive PAP†	8 (17%)	6 (25%)
Anesthesia/analgesia		
Not reported†	13 (28%)	5 (22%)
Regional techniques†	22 (47%)	8 (35%)
General anesthesia†	12 (25%)	7 (30%)
Local anesthesia/analgesia†	0	3 (13%)
Oxytocic drugs†	14 (30%)	4 (17%)
Antithrombotic therapy†	28 (60%)	12 (46%)
Neonatal survival†	43 (96%)§	20 (77%)
95% CI	85-99	56-91
Maternal death, days postpartum (n = 23)	—	5 (0-30)‡

Data presented are *mean value ± SD (range); †number (%) of patients; or ‡median value (range). §In two cases neonatal outcome was not reported. ||Three patients died before delivery and 23 died after delivery. CI = confidence interval; CVP = central venous pressure; PAP = pulmonary artery pressure; SAP = systemic arterial pressure.

Table 4. Management and Outcome of Pregnant Women With Primary Pulmonary Hypertension (n = 27)

	Maternal Survival	Maternal Mortality
No. (%)	19 (70%)	8 (30%)§
95% CI	50-86	14-50
Age (years)*	25.7 ± 5.3 (14-36)	23.3 ± 4.4 (18-31)
Hospital admission (weeks of pregnancy)*	26.9 ± 5.5 (15-36)	28.7 ± 5.9 (18-36)
Toxemia of pregnancy†	1 (5%)	0
Delivery (weeks of pregnancy)*	35.2 ± 3.9 (29-39)	33.3 ± 5.4 (26-40)
Vaginal delivery†	12 (63%)	3 (37%)
Operative delivery†	7 (37%)	5 (63%)
Monitoring		
Not reported†	8 (42%)	4 (50%)
Invasive SAP and/or CVP†	11 (58%)	4 (50%)
Invasive PAP†	9 (47%)	5 (63%)
Anesthesia/analgesia		
Not reported†	8 (42%)	2 (25%)
Regional techniques†	9 (47%)	5 (63%)
General anesthesia†	2 (11%)	1 (13%)
Oxytocic drugs†	7 (37%)	3 (37%)
Antithrombotic therapy†	6 (32%)	3 (37%)
Neonatal survival†	18 (95%)	6 (75%)
95% CI	74-100	35-97
Maternal death, days postpartum§	—	6 (2-35)‡

Data presented are *mean value ± SD (range); †number (%) of patients; or ‡median value (range). §All maternal deaths occurred postpartum. Abbreviations as in Table 3.

boembolism (n = 3), cerebral thromboembolism (n = 1) and rupture and dissection of the pulmonary artery (n = 1). Late maternal death (months postpartum) was reported in two cases. Live-born neonates (n = 66, 90%) weighed 2,112 ± 876 g. Fetal or early neonatal death due to maternal death or decompensation, intrauterine growth retardation and/or premature delivery was reported in six patients (23,26,35,41, 53,56), late neonatal death due to congenital heart disease was reported in three patients (13,28,32) and neonatal outcome of two pregnancies was not reported (22,45). The fetal/neonatal mortality rate in this group was 13% (95% CI 6 to 23).

Primary pulmonary hypertension. The characteristics of 27 parturients (42,61-79) are summarized in Table 1. Dyspnea at rest and, less frequently, a hoarse voice, hemoptysis, syncope, cyanosis or toxemia of pregnancy indicated hospital admission during pregnancy. Treatment consisted of bed rest and oxygen supplementation, digoxin (occasionally), diuretic agents and vasodilators. Peripartum management is presented in Table 4. Eleven parturients (41%) delivered at term, 10 (37%) between 32 and 36 weeks and 6 (22%) ≤31 weeks. Two survivors delivered during hyperbaric oxygenation (76). Major postpartum complications were worsening of dyspnea, cyanosis, hemoptysis, pulmonary hypertensive crisis (in one patient after use of oxytocin) and systemic hypotension. Eight patients (30%) died (61,63,64,66,68,70,72,74), all after delivery (Fig. 1), of therapy-resistant heart failure; only in the case of venoocclusive disease were venous thrombi found at autopsy (68).

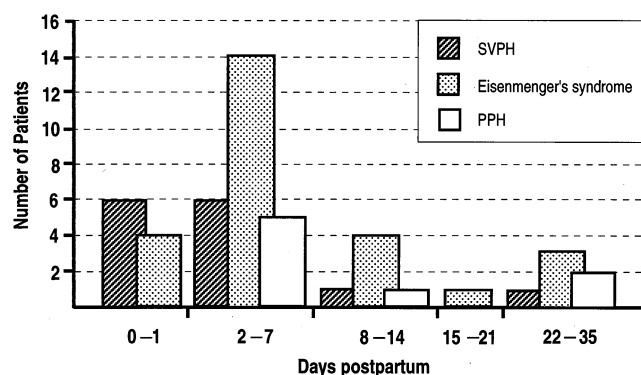


Figure 1. Time of maternal death in parturients with Eisenmenger's syndrome (n = 26), PPH (n = 8) and SVPH (n = 14). The 0-1 day postpartal period includes three patients with Eisenmenger's syndrome who died during pregnancy.

Two late deaths and two heart-lung transplantations were reported months to years after pregnancy. All neonates (weight $1,978 \pm 758$ g) were live-born, but three infants (11% [95% CI 2 to 29]) who were delivered prematurely (66,68,76) subsequently died.

Secondary vascular pulmonary hypertension. The characteristics of 25 parturients (42,72,80-101) are summarized in Table 1. The causes, concomitant findings or assumed triggers of SVPH were Takayasu's arteritis, pulmonary vasculitis of connective tissue (lupus erythematosus, scleroderma), sickle cell disease, illicit and appetite suppressant drugs, chronic pulmonary thromboembolism, hepatitis, dwarfism with congenital hypothyroidism and peripheral pulmonary artery stenoses. Dyspnea, syncope (rarely), chest pain, hemoptysis, systemic hypotension, toxemia of pregnancy or intrauterine growth retardation led to hospital admission during pregnancy. Bed rest and oxygen supplementation and, in a few cases, digoxin, diuretic agents, steroid therapy and nifedipine were used prepartum. All patients, except for one, delivered at ≥ 32 weeks (Table 5). Pulmonary hypertensive crisis after oxytocin use occurred in one patient. One parturient was treated with heparin and urokinase; operative delivery was assisted by extracorporeal circulation; and postpartal treatment with coumarin, nifedipine, prostaglandins and diuretic agents led to the patient's survival (97). All fatalities (Fig. 1) occurred after delivery (42,72,81,83,85,86,89,91-96) and were described as sudden (n = 7) or progressive (n = 7) heart failure; no evidence of new pulmonary thromboembolism was found at autopsy. Late maternal death, several months postpartum, was reported in three patients. Twenty-two neonates (weight $2,372 \pm 640$ g) survived. One stillbirth (81) and two neonatal deaths due to congenital anomalies (88,89) resulted in a fetal/neonatal mortality rate of 12% (95% CI 3 to 31).

Logistic regression analysis (Table 6). This analysis revealed several risk factors in the Eisenmenger's syndrome and SVPH groups and none in the PPH group. Late diagnosis of PVD and timing of hospital admission (risk increasing by 9% with each week of pregnancy) were independent risk factors of

maternal mortality for all patients. Operative delivery, severity of pulmonary hypertension (diastolic rather than systolic PAP) and number of previous pregnancies and deliveries were contributing factors. Analysis of maternal mortality showed a trend toward a significant difference between the PPH and SVPH groups ($p = 0.06$) and between the Eisenmenger's syndrome and SVPH groups ($p = 0.08$). Neonatal outcome was significantly influenced by maternal outcome in patients with Eisenmenger's syndrome ($p < 0.046$, OR 4.5) and cumulatively in all patients ($p < 0.02$, OR 3.8).

Discussion

Eisenmenger's syndrome. In a review of the cases from the late 1940s to 1978, Gleicher et al. (7) found that 30% of all pregnancies in patients with Eisenmenger's syndrome resulted in maternal death. More recently, an 11% mortality rate in a London-Torino bicentric study (102); one maternal death among 26 patients in Trivandrum, India (103); and survival of all five patients in Hamilton, Ontario, Canada (42) implicate that the outcome of pregnancy in patients with Eisenmenger's syndrome generally improved. However, two maternal deaths, one abortion and one successful delivery after surgical correction of congenital heart disease were documented in four women in Memphis, Tennessee (104). Three of 10 patients with Eisenmenger's syndrome died in São Paulo, Brasil (41). The mortality rate of 36% (or 33% if six previous pregnancies

Table 5. Management and Outcome of Pregnant Women With Secondary Vascular Pulmonary Hypertension (n = 25)

	Maternal Survival	Maternal Mortality
n (%)	11 (44%)	14 (56%)§
95% CI	24-65	35-76
Age (years)*	26.1 \pm 3.5 (17-30)	29.4 \pm 3.9 (23-34)
Hospital admission (weeks of pregnancy)*	32.2 \pm 6.3 (21-39)	32.6 \pm 4.5 (24-38)
Toxemia of pregnancy†	1 (9%)	3 (21%)
Delivery (weeks of pregnancy)*	36.3 \pm 2.8 (32-40)	35.9 \pm 4.5 (29-39)
Vaginal delivery†	8 (73%)	4 (29%)
Operative delivery†	3 (27%)	10 (71%)
Monitoring		
Not reported‡	5 (45%)	2 (14%)
Invasive SAP and/or CVP‡	6 (55%)	12 (86%)
Invasive PAP‡	6 (55%)	10 (71%)
Anesthesia/analgesia		
Not reported‡	5 (46%)	4 (28%)
Regional techniques‡	3 (27%)	5 (36%)
General anesthesia‡	2 (18%)	5 (36%)
Oxytocic drugs‡	4 (36%)	2 (14%)
Antithrombotic therapy‡	3 (27%)	10 (71%)
Neonatal survival†	10 (91%)	12 (86%)
95% CI	59-100	57-98
Maternal death, days postpartum§	—	1 (0-30)‡

Data presented are *mean value \pm SD (range); †number (%) of patients; or ‡median value (range). §All maternal deaths occurred postpartum. Abbreviations as in Table 3.

Table 6. Logistic Regression Analysis: p Value and Odds Ratio (95% confidence interval)* for Maternal Outcome as Dependent Variable

Independent Covariable	Univariate Analysis				Multivariate Analysis (all patients)
	Eisenmenger's Syndrome	Primary Pulmonary Hypertension	Secondary Vascular Pulmonary Hypertension	All Patients	
Age (year)	>0.1	>0.1	0.06	>0.1	—
Gravida (n)†	>0.1	>0.1	0.052	0.02	0.09
				1.52 (1.06-2.17)	
Para (n)	>0.1	>0.1	>0.1	0.06	—
Late diagnosis‡	0.003	>0.1	>0.1	0.001	0.002
	6.7 (1.8-24.5)			3.5 (1.6-7.5)	5.4 (2.2-13.4)
Hospital admission‡ (week)	0.009	>0.1	>0.1	0.003	0.01
	1.13 (1.03-1.25)			1.11 (1.04-1.19)	1.09 (1.02-1.19)
PAP, systolic (mm Hg)	0.06	>0.1	>0.1	>0.1	—
PAP, diastolic (mm Hg)	0.01	>0.1	>0.1	0.03	—‡
	1.08 (1.02-1.16)			1.03 (1.00-1.06)	
Operative delivery†	>0.1	>0.1	0.03	0.02	0.07
			6.6 (1.1-38.8)	2.4 (1.1-5.2)	
Anticoagulant drug	>0.1	>0.1	0.03	>0.1	—
			6.6 (1.1-38.8)		

*Odds ratio and 95% confidence interval were calculated at $p < 0.05$. For continuous and counting data, the odds ratios are expressed per unit of measurement.
†Gravida, late diagnosis, hospital admission and operative delivery were included in the multivariate analysis. ‡Diastolic value was excluded from the multivariate analysis owing to a high number of missing values. PAP = pulmonary artery pressure.

are included) indicates that the risks remained rather unchanged over the past two decades of experience with Eisenmenger's syndrome.

Primary versus secondary vascular pulmonary hypertension. The classification of PVD syndrome is controversial (4-6,9,67,105), and PPH is acknowledged to be a pleomorphic disease whose etiology is unclear (106). Hopkins et al. (6) recently found that a more favorable hemodynamic profile and a higher 3-year survival rate are characteristic of patients with Eisenmenger's syndrome as compared with patients with PPH. It was expected that the outcome of late pregnancy between these groups would similarly differ. However, maternal survival was comparable in patients with Eisenmenger's syndrome and the "pure form" of PPH, in contrast to the mortality rate of >50% in patients with SVPH. In addition, the outcome differences were obvious within the heterogeneous group of patients with SVPH. Pulmonary vasculitis due to systemic diseases and illicit drug abuse resulted in maternal death in almost all patients, representing the most malignant form of PVD, with poor tolerance during pregnancy and postpartal changes. On the other extreme, in Takayasu's arteritis and peripheral pulmonary artery stenoses (right ventricular and central pulmonary hypertension with protected pulmonary microcirculation), the pregnancy, delivery and postpartal period were experienced without difficulties.

General risk factors and cofactors. Patient age and history of pregnancy (Table 6) were found to represent potential risk cofactors of maternal death. Although incompletely reported and not measured at identical periods during gestation, available Sao_2 and hemoglobin data failed to show any relation to the outcome in Eisenmenger's syndrome. PAP values were incompletely reported as well, and were not measured using

identical methods or at the identical period of pregnancy. Possibly owing to the missing values, diastolic PAP was a stronger risk cofactor than systolic PAP in the patients with Eisenmenger's syndrome and cumulatively for all patients.

The late diagnosis of PVD and late hospital admission were the independent risk factors of mortality for patients with Eisenmenger's syndrome and cumulatively for all patients. On average, patients with Eisenmenger's syndrome and those with PPH were admitted to the hospital at the beginning of the third trimester (Tables 1, 3 and 4). The average difference in the timing of hospital admission was 5 and 2 weeks between survivors and nonsurvivors in the Eisenmenger and PPH groups, respectively. Patients with SVPH were admitted 5 weeks later, and no difference was found between survivors and nonsurvivors (Tables 1 and 5). Thus, earlier diagnosis and hospital admission and timely preparation of the medical team have favorably influenced the maternal outcome. Although the benefits of nitric oxide and prostacyclin therapy (105,106) in pregnant women with PVD remain to be confirmed, current therapeutic options look more promising than those available in the 1978-1996 period.

Management of late pregnancy and delivery. Duration of pregnancy, timing and mode of delivery, type of anesthesia or analgesia (with a preference for epidural technique) and type of maternal monitoring were similarly distributed between survivors and nonsurvivors. A pulmonary artery catheter was rarely used in patients with Eisenmenger's syndrome and more frequently in those with PPH and SVPH. The peripartal use of a pulmonary artery catheter in PVD must be questioned owing to its limited value of providing monitoring information, its higher potential for complications and its lack of influence on maternal outcome.

Operative delivery was an independent risk factor of maternal mortality in patients with SVPH and a potential risk factor for all patients (Table 6). In many patients sudden death was reported days after delivery, not as a direct consequence of the operation. Although frequently unavoidable, cesarean section should be considered a risk (co)factor as it is not the safest route for delivery (107) in parturients with PVD. The use of antithrombotic drugs remains controversial. These drugs have caused bleeding, cardiovascular instability and ultimately maternal death in some patients. Anticoagulation was even found to be a significant (univariate) risk factor of maternal mortality in patients with SVPH. In contrast, judicious use of antithrombotic drugs contributed to survival in a number of patients with Eisenmenger's syndrome, PPH and SVPH (41,42,52,64,65,73,75,80,99).

Timing of maternal death. The first month after delivery represents the period of highest risk for patients with PVD (Fig. 1). Longitudinal studies in healthy parturients found the lowest myocardial contractility at delivery and immediately postpartum and slow cardiovascular recovery over the next 3 months (108,109). The speculative explanations for predominant postpartal fatalities in PVD include an increased tendency toward thromboembolism, an exaggerated pulmonary vascular reactivity and/or a mismatch between declined myocardial contractility and a too sudden decrease in blood volume after delivery.

Neonatal outcome. Only cases of late pregnancy were reviewed, and no conclusions can be drawn about the overall fetal outcome, particularly of early pregnancy, in women with PVD. A neonatal survival rate of nearly 90% was surprisingly high. If previous pregnancies are considered, the rate is still 82% in the group with Eisenmenger's syndrome. The neonatal outcome depended on maternal tolerance of late pregnancy and the presence of congenital anomalies, and not on the type of PVD. Although these survival data are encouraging, the differences in maternal and neonatal outcome implicate a "conflict of interest" between the pregnant patient with PVD and the fetus.

Study limitations. The published data offered only a limited amount and quality of information. A larger number of prospectively studied patients would provide a precise pattern of hemodynamic changes, differentiate the risks of pregnancy and eventually provide an optimal plan of peripartal management. However, the incidence of PVD in late pregnancy is relatively low. Our systematic search revealed 125 cases reported in the last two decades, and only a few reports provided detailed information on a series of patients. Some reports, perhaps including many patients, remain unpublished, and it is speculative whether the bias to report a successful outcome is balanced by the negative selection of the most severe cases of PVD. The review is a quantitative summary of experiences from various institutions and countries, and the results should be seen as best available global estimates of the management and outcome of late pregnancy in women with PVD.

Conclusions. The outcome of pregnant women with Eisenmenger's syndrome in the last two decades has not changed

compared with the period before 1978. Maternal mortality rates of 30% to 36% were almost identical in patients with PPH and Eisenmenger's syndrome, whereas the rate was relevantly higher (>50%) in those with SVPH. Late diagnosis and late hospital admission were strong independent risk factors of maternal mortality. Operative delivery, severity of pulmonary hypertension, number of previous pregnancies and deliveries and indiscriminate use of anticoagulant drugs must be considered as contributing risk factors. Almost all maternal deaths occurred early after delivery; thus, intensive medical therapy and care should be employed in the highly vulnerable postpartal period in women with PVD.

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